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Review

# No improvement in neurocognitive outcomes after off-pump versus on-pump coronary revascularisation: a meta-analysis

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**Summary**

The popularity of off-pump (beating heart) coronary artery bypass grafting (CABG) was initially stimulated by numerous theoretical benefits including lower incidence of stroke and neurocognitive dysfunction. With a postoperative stroke rate of less than 1% for elective CABG, it has been very difficult to demonstrate any significant differences in this outcome between techniques. However, changes in neurocognitive function are more common in the postoperative setting and thus provide greater power for demonstrating improvement with changes in surgical technique. The aim of this meta-analysis was to assess whether there were significant differences in neurocognitive outcomes in patients after undergoing off-pump versus on-pump CABG. A database search for prospective randomised controlled trials of off-pump versus on-pump CABG in any language was conducted. Eight trials incorporating 892 patients fulfilled all the inclusion criteria for reporting of neurocognitive outcomes, and were able to be included in this meta-analysis. Sufficient data were available across the seven studies to combine results for five neurocognitive tests (Rey Auditory Verbal Learning, Grooved Pegboard, Trail A and B, and Digit Symbol). Overall there were no convincing differences in outcomes in neurocognitive testing between off-pump and on-pump CABG groups. The results of this meta-analysis show that there are no significant neurocognitive benefits when comparing off-pump versus on-pump CABG.


*Keywords:* Meta-analysis; Neurologic manifestations; Coronary artery bypass; Off-pump

## 1. Introduction

There has been intense debate regarding the benefits of off-pump coronary revascularisation in comparison to more traditional techniques using the cardiopulmonary bypass circuit and cardiac arrest. Off-pump surgery techniques maintain pulsatile flow, and avoid passing blood through a synthetic circuit and oxygenator, thus reducing activation of the coagulation and inflammatory cascades [1,2]. Further, the use of the cardiopulmonary bypass circuit has been associated with cerebral microemboli and could potentially be avoided by the use of off-pump techniques [3,4].

In addition, off-pump coronary revascularisation involves less handling of the often atheromatous ascending aorta. This reduces the incidence of microemboli that have been shown to occur at the time of application and particularly with release of the aortic cross-clamp or side-biting clamp [4].

Until recently, no systematic review was able to demonstrate stroke reduction with off-pump coronary revascularisation. However, a meta-analysis recently published by Sedrakyan and colleagues [5] was able to demonstrate a 50% relative risk reduction of stroke using off-pump techniques compared to on-pump coronary artery bypass graft (CABG) surgery. Because the incidence of stroke is very low following CABG (generally under 1%), it has been difficult to demonstrate a significant reduction in stroke incidence after off-pump surgery in individual trials [6]. For this reason, investigators have looked to more subtle neurological changes following surgery such as neurocognitive decline. However, even these results have varied widely between individual trials. No previous systematic review has specifically analysed the results of neurocognitive outcomes following off-pump versus on-pump CABG. The purpose of this meta-analysis therefore was to assess these outcomes.

## 2. Methods

This meta-analysis was conducted using the recommendations made in the QUOROM statement as a guide [7].

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### 2.1. Search strategy

All published prospective randomised controlled trials assessing neurocognitive outcomes after off-pump versus on-pump coronary revascularisation were considered. Studies were compiled from systematic literature searches of databases including Cochrane (reviews and registry of controlled trials), Medline and PsycINFO for the last twenty years up until September 2007.

The search strategy included the terms 'off-pump coronary revascularisation', 'off-pump coronary artery bypass', 'randomised' controlled trial, 'controlled clinical trial' and combinations of 'neurocognitive outcomes', 'neurocognitive tests' and 'brain function'. All studies were then reviewed to determine if they had included neurocognitive outcomes as an endpoint. A search of other reviews of coronary revascularisation techniques was also conducted, checking reference lists of these articles also for further relevant studies. The search was also repeated at regular intervals during this systematic review to ensure any new publications were captured. The search strategy included all languages. The search was conducted by both the first and second authors who also reviewed the papers and culled the list according to the entry criteria of this search.

### 2.2. Inclusion and exclusion criteria

Prospective randomised trials comparing off-pump versus on-pump coronary artery revascularisation were included, whereby patients were randomly assigned to either off-pump or on-pump CABG. All patient populations were considered eligible. Neurocognitive testing as an endpoint in the study was a prerequisite. All language publications were considered eligible.

Exclusions were made where the trials were found to be not truly randomised, where brain function assessments were performed using magnetic resonance imaging or cerebral microemboli markers as opposed to neuropsychological testing. Also excluded were studies not conforming to the recommended 'consensus statement' on neurocognitive outcomes testing and reporting after cardiac surgery [8].

Where there was insufficient data reported on the neurocognitive tests to obtain means and standard deviations, the corresponding authors of those papers were contacted.

### 2.3. Data extraction

A standard neurocognitive test battery was used in the eight included studies, conforming to the consensus statement of neurocognitive testing after cardiac surgery [8]. Not all papers reported all tests, rather a selection of tests to assess each cognitive domain. However, some papers had data missing (e.g. baseline figures which were not published, or data which was represented graphically only), and all of these primary authors were contacted to request this information.

After completing the search strategy as outlined above, the relevant data were extracted from the identified papers by two reviewers working together (SFM, LNS).

### 2.4. Endpoints

The endpoints used in this meta-analysis were short term (less than or equal to 3 months) and long-term (greater or equal to 6 months) neurocognitive performance of cardiac surgery patients, after undergoing off-pump or on-pump CABG. Where authors had tested patients at two time points within the first three postoperative months, the later time point was used.

### 2.5. Statistical analysis

The outcomes were analysed as continuous variables and the mean and standard deviations were available for all data used. The weighted mean difference was calculated for each outcome. The meta-analysis was performed using Review Manager (RevMan) Version 4.2 for Windows. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003). Heterogeneity was explored by calculating the $I^2$ statistic to quantify the degree of heterogeneity across the trials that could not be attributed to chance alone. For each analysis, the fixed effect (precision weighted) or random effects (Der-Simonian and Laird) model was chosen depending on the degree of heterogeneity. Statistical significance was defined as two-sided $p < 0.05$. Publication bias was assessed using funnel plots.

Post hoc sample size analysis showed that there were sufficient numbers to detect a 6% difference in test results (averaged across all five neurocognitive tests) with a power of 0.8 and type II error of $<0.05$.

## 3. Results

Eighty-three studies were identified by the initial literature search, which included a review of all references of other systematic review articles comparing off-pump to on-pump surgery (although with different endpoints). The abstracts or full articles of all these studies were reviewed and 59 studies were able to be excluded because they were either case studies, retrospective reviews, compared off-pump surgery to percutaneous interventions, or were review articles.

Twenty-four studies were initially identified for possible inclusion in the meta-analysis [9–32]. Corresponding authors were contacted where further clarification of study design (randomisation techniques, or duplication of data) were required, and where there was insufficient reporting and further data was required for inclusion into the meta-analysis. Of the 10 authors contacted, seven replied and two were able to forward further data to enable inclusion in the meta-analysis [25,31]. Of the 24 studies initially identified for possible inclusion in the meta-analysis, 16 were rejected and are listed in Table 1 [9–24]. The primary endpoints in those trials and the reasons for exclusion are also listed.

The eight studies which were included, along with the study design are outlined in Table 2 [25–32]. The study population demographics are outlined below in Table 3. Analysis by funnel plot showed no significant publication bias.

The eight trials in this meta-analysis included 892 patients. Five neurocognitive tests were able to be analysed,

Table 1
Excluded studies

| No. | Year of publication | Author | Randomised study | No. of patients | Primary endpoints | Reason for exclusion from current meta-analysis |
|---|---|---|---|---|---|---|
| 1 | 2000 | Westaby et al. [9] | No | 100 | S-100β levels and neuropsychological measures | No off-pump group and insufficient reporting of neurocognitive measures |
| 2 | 2000 | Diegeler et al. [10] | Yes | 40 | Transcranial Doppler to assess HITS, S-100β levels and neuro-psychological testing | Standard neurocognitive tests not used |
| 3 | 2000 | Lloyd et al. [11] | Yes | 60 | Neuropsychological testing and S-100β levels | Insufficient reporting of neurocognitive measures |
| 4 | 2003 | Lund et al. [12] | Yes | 52 | Transcranial Doppler to assess HITS, cerebral MRI and neuro-psychological testing | Data contained in later publication |
| 5 | 2003 | Schmitz et al. [13] | No | 251 | Neurocognitive testing | Non randomised |
| 6 | 2003 | Keizer et al. [14] | Yes | 81 | Neurocognitive testing | Neurocognitive testing did not follow consensus statement |
| 7 | 2004 | Van Dijk et al. [15] | Yes | 281 | Neurocognitive testing | Contained data on previous published results |
| 8 | 2005 | Ascione et al. [16] | Yes | 20 | Fluorescein angiography and transcranial Doppler to assess HITS | No neurocognitive testing |
| 9 | 2005 | Stroobant et al. [17] | No | 50 | Transcranial Doppler to assess HITS and cerebral blood flow velocity | Non randomised |
| 10 | 2005 | Kobayashi et al. [18] | Yes | 167 | 3-Year cardiac events. Secondary endpoints of completeness of revascularisation, early clinical outcomes and neurocognitive function | S100 and neuron-specific enolase reported but no neurocognitive testing |
| 11 | 2005 | Diephius et al. [19] | Yes | 175 | Jugular bulb desaturation | No neurocognitive testing |
| 12 | 2006 | Jensen et al. [20] | Yes | 120 | Neuropsychological testing | Insufficient reporting of neurocognitive measures (no means or standard deviations) |
| 13 | 2006 | Chernov et al. [21] | No | 65 | Brain SPECT scanning, neurocognitive testing | Non randomised |
| 14 | 2006 | Bonacchi et al. [22] | Yes | 42 | S-100β levels and neuron-specific enolase | No neurocognitive testing |
| 15 | 2007 | Biancari et al. [23] | No | 1016 | Stroke score risk | Non randomised |
| 16 | 2007 | Motallebzadeh et al. [24] | Yes | 212 | Neurocognitive testing and transcranial Doppler to assess HITS | Insufficient reporting of neurocognitive measures |

SPECT: single photon emission computed tomographic scan; MRI: magnetic resonance imaging; HITS: high-intensity transient signals.
Trials excluded from meta-analysis.

as there were enough studies which included these particular tests. The tests and the respective cognitive domain assessed were: Rey Auditory Verbal Learning (verbal memory), Grooved Pegboard (motor capacity), Trail A and B (divided attention and executive function), and the WAIS III Digit Symbol test (information processing). The other tests were not consistently used by enough of the studies to have sufficient data to combine. Results were available at baseline, less than 3 months postoperatively and between 6 and 12 months postoperatively for these three cognitive domains.

The results of the Rey Auditory Verbal Learning test (Fig. 1) show no significant differences between those patients who underwent off-pump or on-pump coronary revascularisation either at baseline, in the first 3 months postoperatively or between 6 and 12 months postoperatively. There was also no significant change between baseline and the two postoperative time points in either group. No significant heterogeneity was noted at baseline or at the less than 3 months testing. However, there was significant heterogeneity noted at the late neurocognitive testing (6–12 months) with an $I^2$ of 79.8% ($p = 0.002$). Re-analysis using a random effects model did not alter the lack of effect of treatment seen with the fixed effects model.

The results of the Grooved Pegboard test showed no significant differences between off-pump and on-pump CAGS at baseline or at either postoperative time point (Fig. 2). Significant heterogeneity was noted in the 3-month time point with an $I^2$ of 68.5% ($p = 0.01$) and again re-analysis using a random effects model did not alter the effect seen.

Meta-analysis of Trail A test data is shown in Fig. 3. In this particular neurocognitive test, significant improvements in function were seen in the off-pump groups at both the early ($z = 2.36$; $p = 0.02$) and late ($z = 4.06$; $p < 0.0001$) time periods. No significant heterogeneity was seen at either time point. The baseline assessment showed no significant differences between groups and no significant heterogeneity.

In contrast, the Trail B test, which assesses a similar domain to the Trail A test, did not show any significant differences between groups at any time point (Fig. 4). Significant heterogeneity was noted at the early post-operative time point $I^2$ of 70% ($p = 0.003$), but not at the other time points. Re-analysis at the early postoperative time point with a random effects model did not show any significant differences between groups.

The final test was the Digit Symbol which showed significant heterogeneity with a fixed effects model, thus a random effects model is presented (Fig. 5). Significant heterogeneity remains at the early postoperative time point ($I^2$ 70.1%; $p = 0.005$), but not the other time points. No differences between groups were noted in the test results at any time point. Interestingly, after removal of the study by Lee et al. [28], which is a significant outlier, the pooled results showed no significant heterogeneity, and significant differences in favour of the off-pump group at both the baseline ($z = 2.42$; $p = 0.02$) and at the early postoperative time point ($z = 2.56$; $p = 0.01$) [25].

Table 2
Included studies

| No. | Year of publication | Author | No. of patients | Primary endpoints | Randomisation and allocation method | Allocation concealed[a] | Intention to treat analysis? | Loss to follow up (no. of patients/% of group)[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | 2001 | Baker et al. [25] | 26 | Troponin T and neuropsychological testing | Not described | Not clear | No crossover | 4 (33%) off-pump<br>4 (29%) on-pump |
| 2 | 2002 | Zamvar et al. [26] | 60 | Neurocognitive testing | Computer generated/ sealed envelope | Yes | No crossover | None |
| 3 | 2002 | Van Dijk et al. [27] | 281 | Neurocognitive testing | Computerised block randomisation/telephone | Not clear | Yes (15 crossovers) | 12 (8%) off-pump<br>17 (12%) on-pump |
| 4 | 2003 | Lee et al. [28] | 60 | Neurocognitive testing, whole brain SPECT, transcranial Doppler to assess HITS | Sealed envelope | Yes | No crossover | 3 (10%) off-pump<br>4 (13%) on-pump |
| 5 | 2005 | Lund et al. [29] | 120 | Neurocognitive testing and cerebral MRI | Block randomisation | Yes | Yes (7 crossovers) | 6 (10%) off-pump<br>8 (13%) on-pump |
| 6 | 2006 | Al-Ruzzeh et al. [30] | 164 | Angiographic graft patency and neurocognitive function | Computer generated | Yes | No crossover | 11 (13%) off-pump<br>12 (14%) on-pump |
| 7 | 2006 | Ernest et al. [31] | 107 | Neurocognitive testing | Computer generated/ sealed envelope | Yes | Yes (1 crossover only) | 14 (23%) off-pump<br>14 (30%) on-pump |
| 8 | 2006 | Vedin et al. [32] | 70 | Neurocognitive testing | Not described | Not clear | Yes (3 crossovers) | 3 (9%) off-pump<br>5 (14%) on-pump |

Trials included in meta-analysis.
[a] Blinded to neuropsychologist examiner.
[b] loss to follow up at latest testing period.

Table 3
Demographics of patients in included studies

| | Treatment group | Author and reference number | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Baker et al. [25] | Van Dijk et al. [26] | Zamvar et al. [27] | Lee et al. [28] | Lund et al. [29] | Al Ruzzeh et al. [30] | Ernest et al. [31] | Vedin et al. [32] |
| | | Year of publication | | | | | | | |
| | | 2001 | 2002 | 2002 | 2003 | 2005 | 2006 | 2006 | 2007 |
| | | Number of patients | | | | | | | |
| | | *N* = 26 | *N* = 281 | *N* = 60 | *N* = 60 | *N* = 120 | *N* = 168 | *N* = 107 | *N* = 70 |
| Age (years) (mean ± SD) | Off-pump | 61.7 ± 11.7 | 61.7 ± 9.2 | 63.5 ± 9.1 | 65.5 ± 9.6 | 64.8 ± 7.8 | 63.1 ± 11 | 63.2 ± 9.0 | 65.0 ± 9.1 |
| | On-pump | 65.9 ± 8.3 | 60.8 ± 8.8 | 61.6 ± 10 | 66 ± 11.2 | 65.2 ± 8.4 | 63.1 ± 9.6 | 63.7 ± 10.7 | 65.0 ± 9.1 |
| Gender (male %) | Off-pump | 92 | 66 | 83 | 80 | 85 | 83 | 78 | 78 |
| | On-pump | 71 | 71 | 90 | 73 | 72 | 84 | 81 | 84 |
| Diabetes (%) | Off-pump | 11 | 9 | NR | 20 | NR | 24 | 27 | 18 |
| | On-pump | 30 | 17 | NR | 37 | NR | 21 | 31 | 19 |
| Hypertension (%) | Off-pump | 56 | 40 | NR | 70 | 42 | 62 | 79 | 52 |
| | On-pump | 70 | 44 | NR | 87 | 43 | 55 | 79 | 46 |
| Previous stroke (%) | Off-pump | 0 | 4 | Excluded | 7 | 8.3 | NR | 7.1 | 3 |
| | On-pump | 0 | 3 | Excluded | 3 | 6.6 | NR | 3.6 | 0 |
| Education (years) | Off-pump | NR | NR | NR | 11.7 | 9.9 | NR | 11.0 | 13.3 |
| | On-pump | NR | NR | NR | 13.0 | 8.3 | NR | 11.9 | 12.7 |

NR: not reported.
Demographics of patients in included trials.

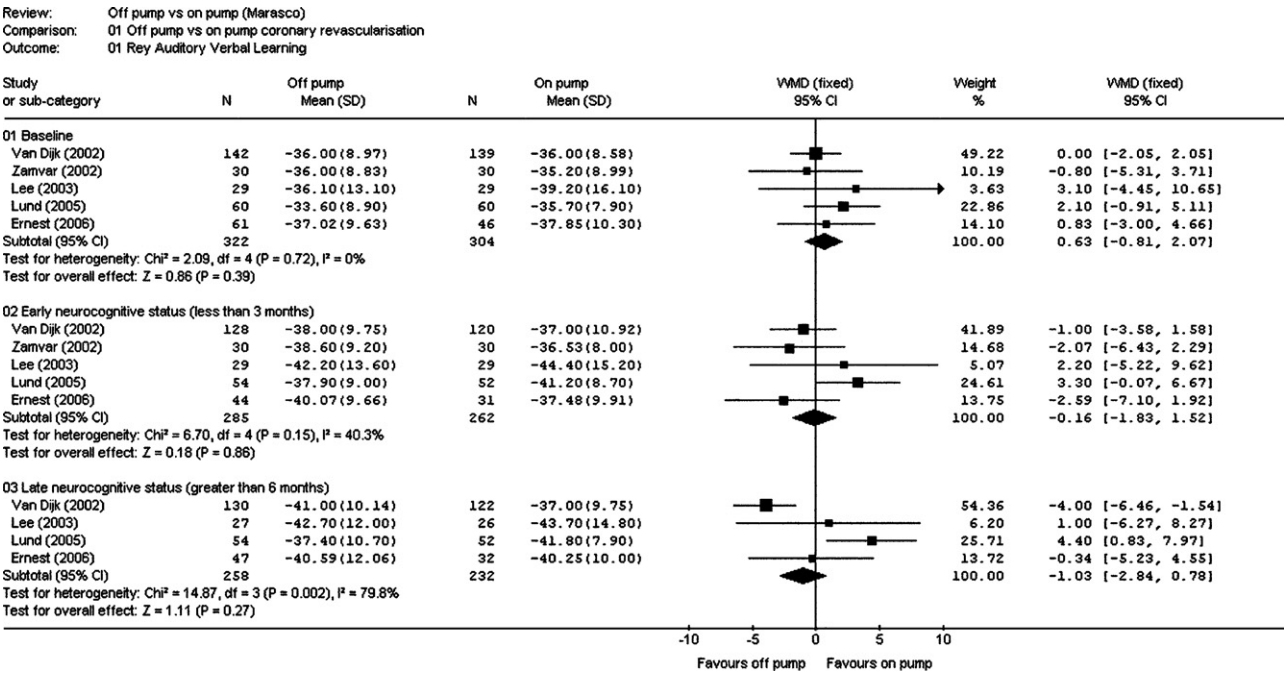


Fig. 1. Meta-analysis of Rey Auditory Verbal Learning.

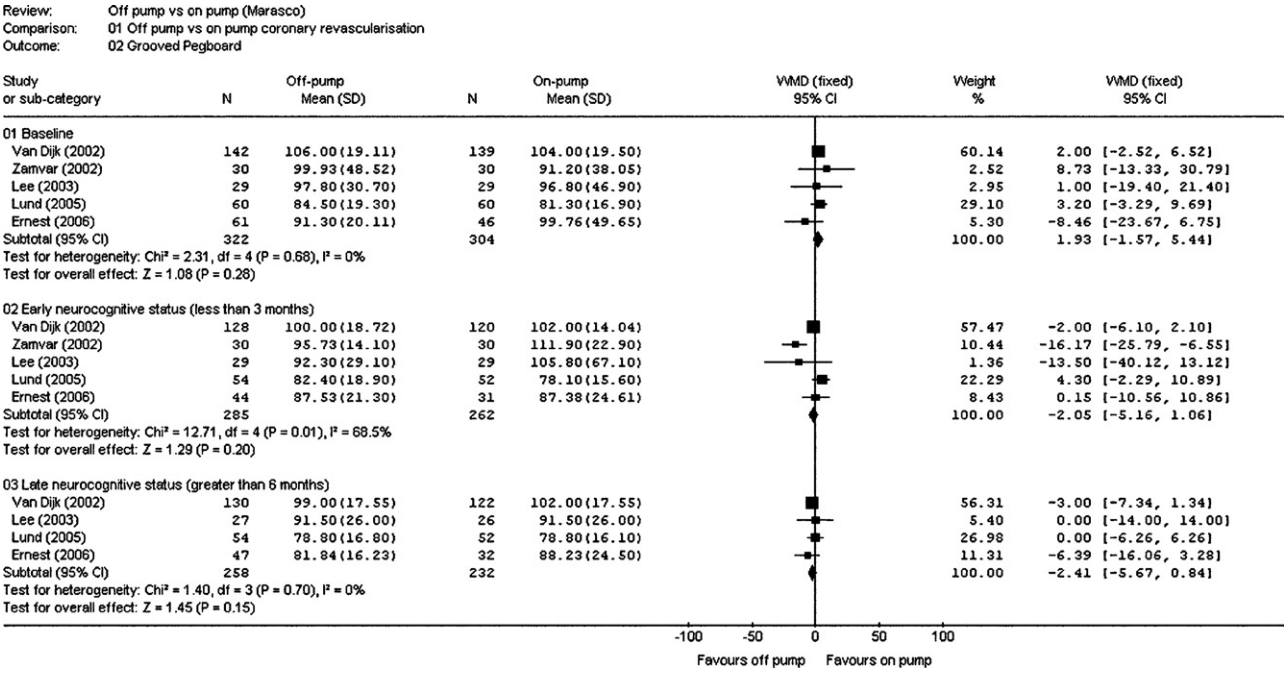


Fig. 2. Meta-analysis of Grooved Pegboard test.

## 4. Discussion

Overall this systematic review has shown that there is no benefit in terms of neurocognitive outcomes in off-pump versus on-pump CABG. Of the five neurocognitive tests analysed, reflecting essentially four different domains, only one test showed any difference between groups. In that neurocognitive test of attention (Trail A), significant improvements were seen in the off-pump group at both the early and late postoperative time points. However, the other test assessing the same general domain of attention and concentration (Trail B) showed no differences between groups at any time point. The discrepancy between these two tests can be explained on the basis of the different aspects of the domains they test. Trail A tests visual attention, with only a small element of scanning, eye-hand coordination and speed involved. Trail B is a much more complex task, incorporating the tasks of Trail A, and including the

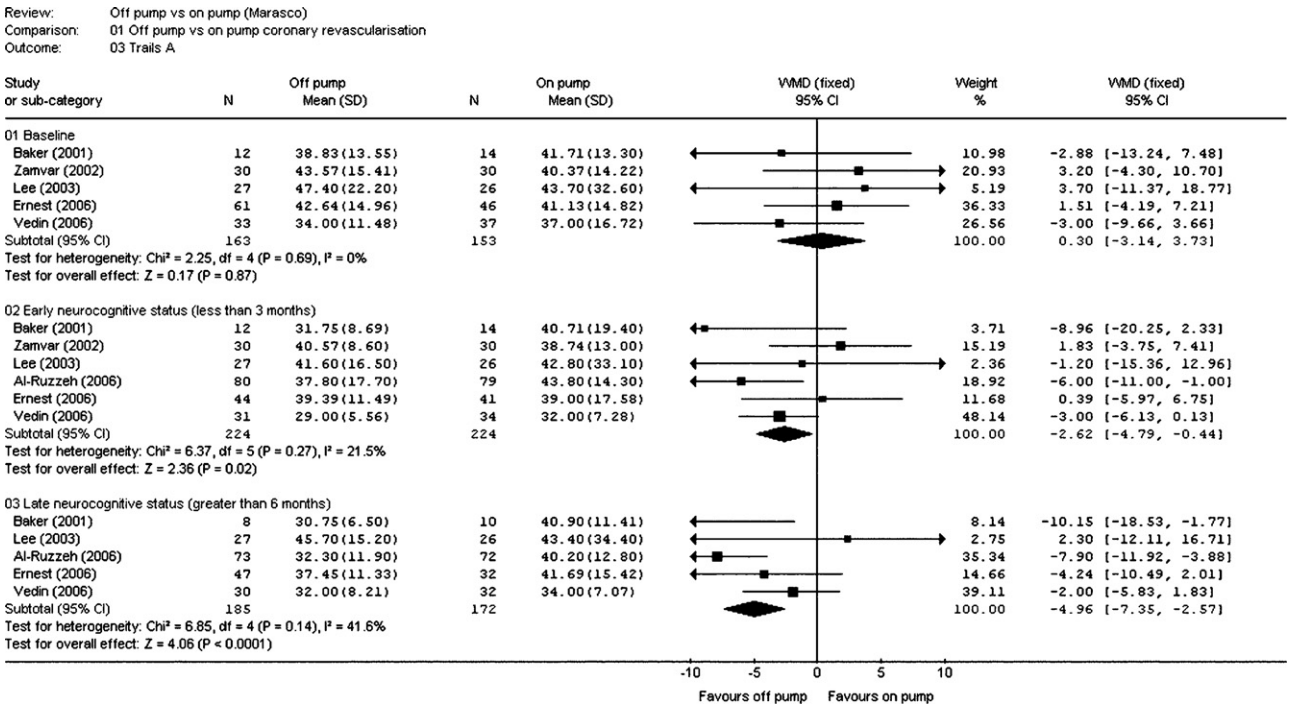


Fig. 3. Meta-analysis of Trail A test.

alternating between letters and numbers (known as complex attention or set shifting). Set shifting is classified under the cognitive domain of executive function or frontal lobe function and is the basis for mental flexibility.

Trail A tends to be a good indicator of general cerebral function and problems with this test indicate reduction in basic attention and speed of processing whereas Trail B is more specific to neuroanatomical areas. Thus it is not

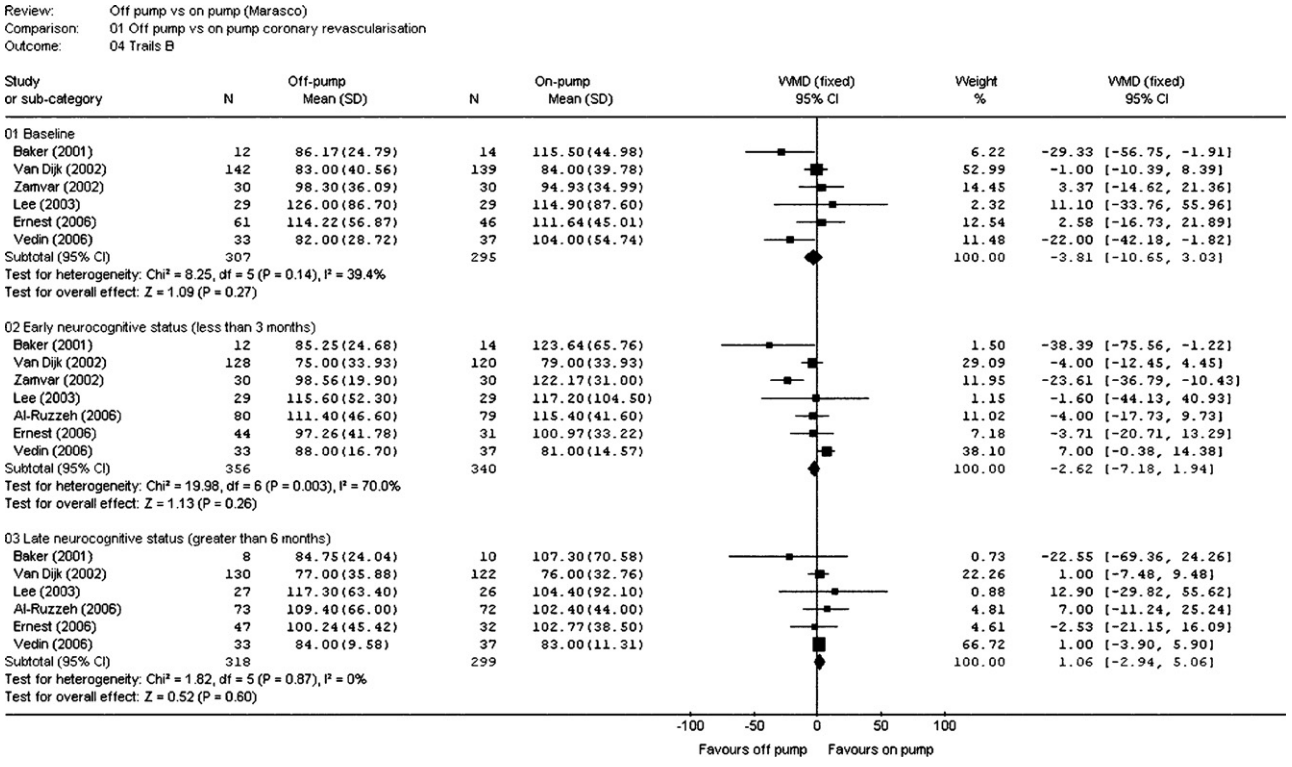


Fig. 4. Meta-analysis of Trail B test.

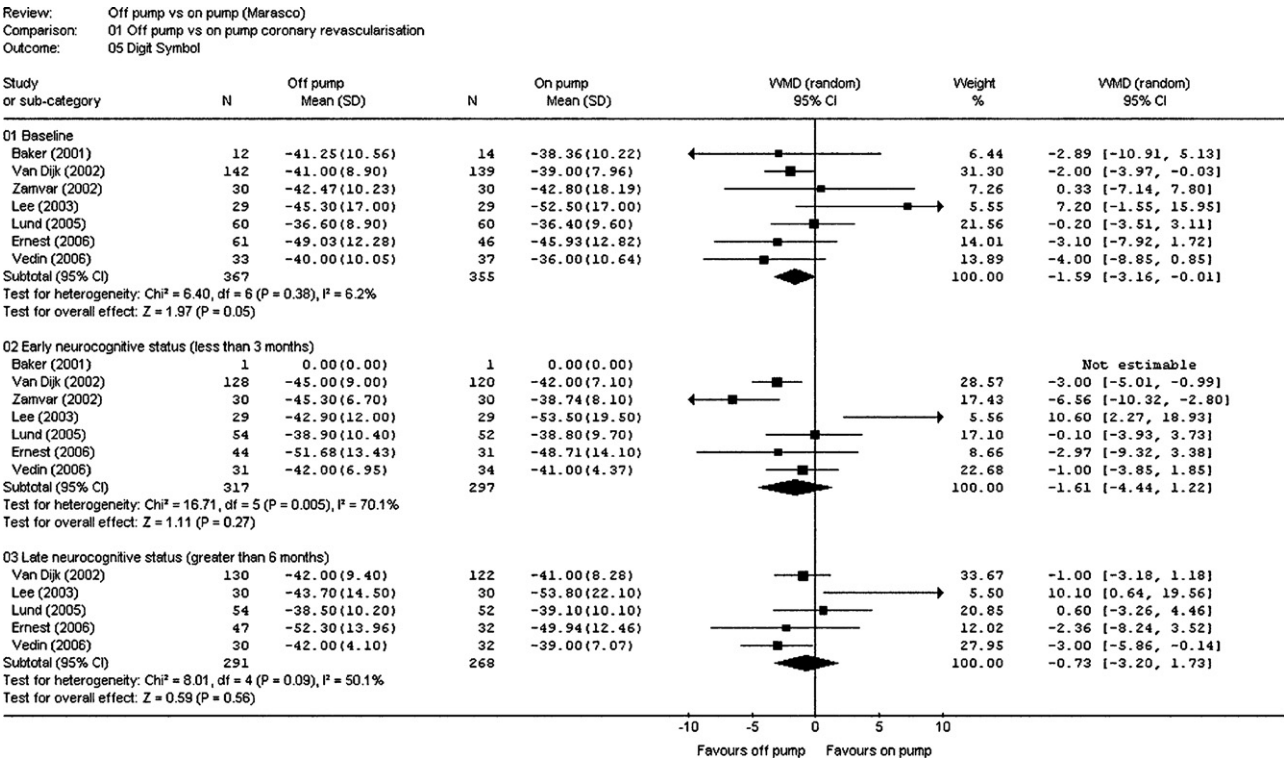


Fig. 5. Meta-analysis of Digit Symbol test.

uncommon to see a discrepancy between the two tests whereby the patient performs better in Trail A due to its more superficial assessment of attention, but performs worse in Trail B because of its more in-depth assessment of this cognitive domain. Further, the sample size in Trail A was smaller than Trail B although a post hoc sample size analysis showed that both tests had enough numbers to detect clinically significant differences (if we take the standard definition that a 20% decline is considered clinically significant).

The only other neurocognitive test which showed some difference between groups was the Digit Symbol test which assesses information processing speed. However, in that analysis the groups were not balanced at baseline, and there was also significant heterogeneity within groups. Re-analysis of the data for that test using a random effects model to account for the large amount of heterogeneity showed no significant differences between groups at any time point.

Our findings confirm the results of most of the individual trials included in the meta-analysis which showed only modest or no differences between groups. The studies by Baker et al. [25], Lund et al. [29], Ernest et al. [31], and Vedin et al. [32] were unable to show any significant differences between off-pump and on-pump CABG groups with neurocognitive testing. Zamvar et al. [26] found significantly worse neurocognitive outcomes in the on-pump CABG group using a definition of neurocognitive impairment as a deterioration of 1SD or more in two or more tests. Nine neuropsychometric tests were administered to all patients in that study of 60 patients. The two largest studies included in this meta-analysis both found some improvements in the off-pump groups [27,30]. The definition of neurocognitive decline is crucial in these types of studies. Lee et al. [28] reported that, compared to baseline, off-pump CABG patients performed better on the Rey Auditory Verbal Learning Test at both the early and late follow-up times. However, when cognitive decline was defined as a 20% decline in 20% of the tests, then there was no difference between groups at either time frame.

The most recent prospective randomised trial on this topic by Motallebzadeh et al. [24] used a composite neurocognitive score to demonstrate better neurocognitive function in the off-pump group at the time of discharge but found no differences between groups at 6 weeks or 6 months postoperatively. We were able to include their unpublished data in our meta-analysis and found no difference in the overall results but a large increase in the heterogeneity. Due to publication restrictions on their unpublished data, we are unable to include it in the meta-analysis presented here.

The recommended core neuropsychological battery of tests lists the Rey Auditory Verbal Learning test, Trail A, Trail B, and the Grooved Pegboard test [8]. All of these tests were included in this meta-analysis. Thus the results reported here give a valid overall assessment of postoperative neurocognitive dysfunction.

One of the main discriminators in assessing the validity of meta-analyses is the degree of heterogeneity in the pooled results. Heterogeneity describes the level of variation in the individual trials. In these meta-analyses, there was no significant heterogeneity at baseline. Significant heterogeneity was seen mainly in the early outcomes (i.e. in the first 3 months postoperatively). This may be due to widely different times of testing within this 3-month window. The times of testing varied from 1 week to 3 months postoperatively in the

studies included. It has been suggested that testing during this timeframe is not meaningful because postoperative neurobehavioural dysfunction is highest in the immediate postoperative period and then declines [8]. This would largely account for the significant amount of heterogeneity seen in the results at this time period. Furthermore, a recent study of neurocognitive function after off-pump CABG has shown that older, anxious patients and those with new onset atrial fibrillation are more likely to have a worse neurocognitive score after surgery [33]. These types of confounding factors could also explain the level of heterogeneity seen, particularly in the early postoperative results.

The cognitive function of candidates for CABG has also been compared to healthy controls and published norms [34]. This has shown that preoperative patients with coronary artery disease have significantly reduced cognitive test scores compared to both healthy controls (matched by age, gender and education) and published norms. Again this may be due to anxiety or depression which has been suggested and refuted by a number of studies [34–36]. Other causative factors have been suggested such as the cardiac disease itself, or associated unrecognised cerebrovascular disease [37,38]. Because mood disturbance has been repeatedly associated with poor neurocognitive performance, concurrent assessment of mood has been recommended in the consensus statement on assessment of neurobehavioural outcomes after cardiac surgery [8]. Despite this, only four of the included studies reported performing a specific assessment of mood [28,30–32].

In general, all of the trials analysed for this meta-analysis were of good quality. However, it appears that in all but one of the studies, an aortic side-biting clamp was used in at least some patients in the off-pump group. This is disappointing as it is well known that manipulation of the aorta is associated with cerebral emboli, and therefore the purported benefits of off-pump surgery (no aortic cannulation, no jet perfusion from the cannula tip, and no aortic cross-clamp) may have been lost [4]. None of the studies reported what percentage of patients had the side-biting clamp applied to the aorta so it is difficult to assess the magnitude of this as a confounding factor. Only one study specifically mentioned that the side-biting clamp was not used in the off-pump group [31]. Another study specifically mentioned that the side-biting clamp was used for every proximal anastomosis in the study which presumably refers to both the off-pump and on-pump groups [29].

Another confounding factor which should be taken into account in such studies is the effect of practice on the test results [39]. This can lead to the phenomenon of regression toward the mean whereby extreme baseline scores tend to become less extreme after repeated testing in the absence of any 'true' change. The statistical phenomenon of regression toward the mean has been found to adversely affect multiple different definitions of cognitive decline. In particular, definitions based on standard deviation (SD):postoperative decline in a subject's performance of more than 1SD of the group's scores before the operation; and the 20% method: decline of more than 20% of the subject's score before the operation, have been shown to be susceptible to this phenomenon [40]. Thus, it has been recommended that group mean scores be analysed as this allows the application of parametric statistical methods which are free from the influence of regression toward the mean. That is why we have followed this approach in this meta-analysis, using group mean data rather than analysing changes from baseline.

Other causes of improvements from baseline scores have been postulated however. It is conceivable that improvements could be a result of the coronary revascularisation, improved cardiac output and improved cerebral blood flow. However, it would be very difficult to demonstrate which of these phenomena would be more responsible for improvements in any particular study. Interestingly it has been shown that after one year postoperatively, cognitive function begins to decline again returning to preoperative levels at 5 years [41].

In terms of the post hoc sample size analysis we have performed, if we use the 20% decline in test result as a clinically significant cut-off, we can see that this meta-analysis has sufficient power to detect much smaller changes. On average, we had sufficient numbers to detect a 6% difference in test results with a power of 0.8 and type II error of $<0.05$.

In concluding that we have been unable to find any clinically relevant neurocognitive benefits to off-pump surgery, we have also assessed the clinical relevance of the limits of our confidence intervals. We have compared our results to published results of the minimum clinically important difference (MCID) [42]. This is defined as the smallest difference in result which can be perceived by the patient and is therefore clinically relevant. Unfortunately this score has not been published in a cohort of cardiac surgery patients to our knowledge. However, by comparing our confidence intervals to the published MCID for both the Grooved Pegboard and Digit Symbol tests in a group of epilepsy patients, we note that our confidence intervals lie well within the MCID for both of these tests.

There has been a recent move away from off-pump surgery because of lack of evidence of benefits. When off-pump surgery was initially developed in 1990s, the proposed benefits were numerous. Interestingly the impetus for off-pump surgery seemed to be largely driven by industry rather than the consumer. After an initially enthusiastic reception by surgeons, the lack of evidence substantiating these proposed benefits has tempered the use of this technique. Further, the patients who are most suitable for this type of surgery (single or double vessel disease) are referred less and less by cardiologists because these patients are also eminently suitable for stenting and other percutaneous interventional techniques.

Other reviews have looked at other endpoints comparing off-pump to on-pump CABGs and found few significant differences. A recent scientific statement from the American Heart Association reports that the current findings consistently favouring off-pump CABG surgery are less bleeding and fewer requirements for blood transfusion. There is little evidence of other significant benefits. In contrast, on-pump CABG is less technically demanding and has a shorter learning curve [43]. That statement was published in 2005 and at that time there was no systematic review based on randomised trials to show a substantial stroke reduction in off-pump versus on-pump CABG.

However, in 2006 a meta-analysis looking at stroke as the main endpoint was published which showed that off-pump

CABG is associated with a 50% reduction in the relative risk of stroke (RR 0.50; 95% CI, 0.27—0.93) [5]. Stroke was reported in 27 trials and evaluated in 3062 patients. That paper also found a 30% reduction in atrial fibrillation (RR 0.70; 95% CI, 0.57—0.84) and a 48% reduction in wound infection (RR 0.52; 95% CI, 0.37—0.74).

A meta-analysis looking specifically at cognitive decline after off-pump versus on-pump CABG was published during the preparation of this manuscript. Interestingly they did not include two RCTs we have included in this manuscript with unpublished data from the authors [44]. Two papers they did include however, we chose to exclude due to failure to conform to the consensus statement of cognitive testing after CABG [10] and reporting of cognitive outcomes as the number of deteriorations per group (susceptible to regression toward the mean) without reporting group means [11]. (We were unable to obtain raw data from the last author). Despite the less rigorous inclusion criteria, the meta-analysis by Tagaki et al. also failed to find any significant differences between groups within 2 weeks or at 6—12 months.

In conclusion, this meta-analysis comparing neurocognitive outcomes between patients undergoing off-pump versus on-pump CABGs has found that there is no clinically relevant difference between groups either early (less than 3 months) or late (6—12 months) after surgery. Future studies examining this outcome should aim to employ a technique of no aortic handling at all to minimise confounding factors. Neurocognitive testing and reporting of results should follow the guidelines suggested by the consensus statement, and detailed data should be included in publications rather than summarised data [8]. A multicentre prospective randomised clinical trial is currently underway aiming to enrol 2200 patients into either off-pump or on-pump arms [45]. The secondary outcomes in that trial include neurocognitive testing at baseline and at one year. If follow-up rates are good, this trial will hopefully add important data to our current knowledge of neurocognitive outcomes after off-pump CABG.

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